Dosimetric comparison of protons vs photons in re-irradiation of intracranial meningioma

Poel, Robert ; Stuessi Lobmaier, Anja ; Andratschke, Nicolaus ; Unkelbach, Jan ; Tanadini-Lang, Stephanie ; Guckenberger, Matthias ; Foerster, Robert

Abstract: <jats:sec>Objectives: Re-irradiation of recurrent intracranial meningiomas represents a major challenge due to dose limits of critical structures and the necessity of sufficient dose coverage of the recurrent tumor for local control. The aim of this study was to investigate dosimetric differences between pencil beam scanning protons (PBS) and volumetric modulated arc therapy (VMAT) photons for intracranial re-irradiation of meningiomas. </jats:sec><jats:sec>Methods: Nine patients who received an initial dose gt;50 Gy for intracranial meningioma and who were re-irradiated for recurrence were selected for plan comparison. A volumetric modulated arc therapy photon and a pencil beam scanning proton plan were generated (prescription dose: 15 × 3 Gy) based on the targets used in the re-irradiation treatment. </jats:sec><jats:sec>Results: In all cases, where the cumulative dose exceeded 100 or 90 Gy, these high dose volumes were larger for the proton plans. The integral doses were significantly higher in all photon plans (reduction with protons: 48.6%, p lt; 0.01). In two cases (22.2%), organ at risk (OAR) sparing was superior with the proton plan. In one case (11.1%), the photon plan showed a dosimetric advantage. In the remaining six cases (66.7%), we found no clinically relevant differences in dose to the OARs. </jats:sec><jats:sec>Conclusions: The dosimetric results of the accumulated dose for a re-irradiation with protons and with photons were very similar. The photon plans had a steeper dose falloff directly outside the target and were superior in minimizing the high dose volumes. The proton plans achieved a lower integral dose. Clinically relevant OAR sparing was extremely case specific. The optimal treatment modality should be assessed individually. </jats:sec><jats:sec>Advances in knowledge: Dose sparing in re-irradiation of intracranial meningiomas with protons or photons is highly case specific and the optimal treatment modality needs to be assessed on an individual basis. </jats:sec>

DOI: https://doi.org/10.1259/bjr.20190113

BJR

https://doi.org/10.1259/bjr.20190113

Received: 30 January 2019 | Revised: 19 May 2019 | Accepted: 28 May 2019

Cite this article as:
Poel R, Stuessi Lobmaier A, Andratschke N, Unkelbach J, Tanadini-Lang S, Guckenberger M, et al. Dosimetric comparison of protons vs photons in re-irradiation of intracranial meningioma. *Br J Radiol* 2019; **92**: 20190113.

FULL PAPER

Dosimetric comparison of protons vs photons in re-irradiation of intracranial meningioma

[1,2]ROBERT POEL, MSc, [1]ANJA STUESSI LOBMAIER, MSc, [1]NICOLAUS ANDRATSCHKE, MD, [1]JAN UNKELBACH, PhD, [1]STEPHANIE TANADINI-LANG, PhD, [1]MATTHIAS GUCKENBERGER, MD and [1]ROBERT FOERSTER, MD

[1]Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland
[2]Center for Proton Therapy, Paul Scherer Institute (PSI), Villingen, Switzerland

Address correspondence to: Dr. Robert Foerster
E-mail: *robert.foerster@usz.ch*

Objectives: Re-irradiation of recurrent intracranial meningiomas represents a major challenge due to dose limits of critical structures and the necessity of sufficient dose coverage of the recurrent tumor for local control. The aim of this study was to investigate dosimetric differences between pencil beam scanning protons (PBS) and volumetric modulated arc therapy (VMAT) photons for intracranial re-irradiation of meningiomas.
Methods: Nine patients who received an initial dose >50 Gy for intracranial meningioma and who were re-irradiated for recurrence were selected for plan comparison. A volumetric modulated arc therapy photon and a pencil beam scanning proton plan were generated (prescription dose: 15 × 3 Gy) based on the targets used in the re-irradiation treatment.
Results: In all cases, where the cumulative dose exceeded 100 or 90 Gy, these high dose volumes were larger for the proton plans. The integral doses were significantly higher in all photon plans (reduction with protons: 48.6%, $p < 0.01$). In two cases (22.2%), organ at risk (OAR) sparing was superior with the proton plan. In one case (11.1%), the photon plan showed a dosimetric advantage. In the remaining six cases (66.7%), we found no clinically relevant differences in dose to the OARs.
Conclusions: The dosimetric results of the accumulated dose for a re-irradiation with protons and with photons were very similar. The photon plans had a steeper dose falloff directly outside the target and were superior in minimizing the high dose volumes. The proton plans achieved a lower integral dose. Clinically relevant OAR sparing was extremely case specific. The optimal treatment modality should be assessed individually.
Advances in knowledge: Dose sparing in re-irradiation of intracranial meningiomas with protons or photons is highly case specific and the optimal treatment modality needs to be assessed on an individual basis.

INTRODUCTION

Meningiomas represent one third of all primary brain tumors. Roughly, 20% of these recur locoregionally after initial treatment and require additional treatment. In many recurrences, after primary radiotherapy (RT), re-irradiation with or without prior salvage surgery is considered. Recurrent meningiomas are thought to have a higher radio resistance than tumors controlled after primary treatment, therefore, requiring adequate doses in the recurrence situation for sufficient local control.[1,2] However, dose delivery is limited by the surrounding organs at risk (OARs) and their regeneration potential after an initial course of radiation remains uncertain. One frequently observed sequel after intracranial re-irradiation is brain barrier disorder.[1,3–5] It has been suggested, based on animal studies, that brain tissue partially repairs damage after an initial course of radiation,[6,7] but the radiobiological background of radiation damage to the brain and its recovery is not fully understood. Nevertheless, in a selective group of patients with recurrent brain disease, re-irradiation has proven to be a clinically safe and effective treatment.[1,4,8–12] Additionally, due to the advances in the management of brain tumors, patients' life expectancy and general prognosis have substantially improved. Therefore, a potentially curative salvage treatment has become necessary for these patients. Consequently, in the last decade, the number of publications on re-irradiation has increased to a large body of mainly retrospective studies[1,3,11–22] and recommendation guidelines for the management of glioblastoma and low grade glioma have been established.[23,24]

For intracranial re-irradiation, the aim is not only to adequately treat the area of recurrence, but also to reduce the total dose to critical OARs within the central nervous system as much as possible, *e.g.* optic nerves and brainstem, making highly conformal approaches desirable in

this context. Also, several studies have suggested an improved outcome, with possible higher doses, in more conformal techniques, *i.e.* stereotactic RT and stereotactic radiosurgery.[20,25,26] Consequently, proton RT has to be considered for intracranial re-irradiation. Theoretically, protons are ideally suited to this challenge. Their characteristic Bragg Peak allows for a rapid fall-off of the irradiation dose at the distal edge of the target, sparing normal tissues that have already received high doses from prior RT. In the last decades, several clinical studies have been performed for re-irradiation with protons in patients with lung cancer, head and neck cancer, esophageal cancer, ependymoma, glioma and chordoma.[4,8–10,12,16,17,20–24,26–33] Recently, a study on reirradiation for intracranial recurrent meningioma with particle therapy concluded this was a safe and effective treatment.[34] The clinical results are positively encouraging with respect to tolerance and short-term outcome. Unfortunately, only one study, involving proton re-irradiation in rectal cancer patients, performed a dosimetric comparison between protons and photons.[35]

Up to today, to our best knowledge, there is no dosimetric evaluation of protons *vs* photons available in the intracranial re-irradiation situation. Therefore, we designed this *in silico* planning study to compare protons *vs.* photons for re-irradiation of recurrent meningiomas.

METHODS AND PATIENTS

Patients from the Department of Radiation Oncology, University Hospital Zurich, who were treated with an initial dose exceeding 50 Gy in 1.8 or 2.0 Gy daily fractions with photons and were re-irradiated for a recurrent intracranial meningioma were selected. The plans of the initial RT and the re-irradiation had to be available in our database. Two new re-irradiation plans were prepared, one with photons and one with protons, with a dose prescription of 45 Gy in 3-Gy-fractions relative biological effectiveness (RBE). For both new plans, the accumulated 2-Gy-equivalent dose (EQD2) including the initial treatment was calculated and a dosimetric analysis was performed.

Structure definition

The planning target volume (PTV) of the original re-irradiation was adopted for this planning study. The PTV was defined as the gross tumor volume (GTV) delineated on MRI by a radiation oncologist including a 3.0 mm margin. In addition, the following OARs were delineated for plan dosimetric comparison: brain, brain–brainstem, brainstem, chiasm, cochlea, hippocampi, optic nerves and pituitary gland.[36]

Volumetric modulated arc therapy (VMAT) photon plan

The field arrangements for the *in silico* plan were adopted from the original clinical re-irradiation plan and consisted of multiple non-coplanar 6 MV flattening filter free (FFF) VMAT beams of a TrueBeam linear accelerator with a high definition multileaf collimator (MLC). The dose was adjusted, and the plan was optimized using the PRO optimizing algorithm in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). The dose calculation was performed with the anisotropic analytical algorithm. The calculation grid size was set to 0.15 × 0.15 cm

Pencil beam scanning proton plan

The proton plans were generated with the Eclipse treatment planning system using the ProBeam data provided by Varian. The proton plans consisted of 2– to 4 pencil beam spot scanning fields using a range shifter with a physical thickness of 5 cm to cover superficial target areas at the surface. The detailed beam data are shown in Table 1. Intensity modulated optimization was performed using the nonlinear universal proton optimizer algorithm. Dose calculation was performed using the proton convolution superposition algorithm.[37] Calculation grid size was 0.25 × 0.25 cm with a slice spacing of 0.3 cm. The proton spot spacing was set to 0.425 cm. The sigma of the beam for this proton data ranges from 4 to 15 mm in low energies with the 5 cm range shifter.[38]

Dose prescription and optimization

Both plans were optimized to deliver 3.0 Gy (RBE) dose per fraction up to a total of 45.0 Gy (RBE) to the PTV. The plan was accepted if 95% of the PTV was covered by more than 95% of the prescribed dose. Plans were optimized using normal tissue optimization (NTO) and an accepted maximum dose of 48.0 Gy (RBE). Nearby critical structures were spared as much as possible without compromising the coverage of the target.

Dose accumulation

The initial plan and the new VMAT and proton plans were transferred to MIM v. 6.6.1 (MIM Software, Cleveland, OH). The initial plan had a daily fractionation of 1.8 or 2.0 Gy. For the new re-irradiation plans, EQD2 distributions were calculated using α/β values of 2 for the spinal cord, brainstem, chiasm and optic nerves, and 3 for the remaining normal tissues. Total dose was derived by adding the initial dose distribution and the EQD2 of the recurrence dose distribution.

Analyses

For the accumulated dose distribution, we analyzed the maximum point dose and mean dose to all defined OARs. The accumulated doses to these critical structures for all patients are grouped and were compared for protons and photons. Additionally, the volume receiving more than 100 Gy (V100) outside the PTV was determined as well as the volumes receiving 90 Gy (V90) and 72 Gy (V72). Furthermore, we analyzed the re-irradiation plans with respect to integral dose and the mean total dose to the brain excluding the PTV. The integral dose is defined as the mean dose received by the body structure multiplied by the volume in liters of the body structure. The Wilcoxon signed-ranks test was performed for statistical analysis on the whole population. *Pp*-values of less than 0.05 were considered statistically significant. Due to the case by case specificity in this patient group, an individual comparison of photons *vs* protons was performed to determine in which specific cases protons could be beneficial. All statistical analyses were performed with Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

Table 1. Conformity index and proton beam orientation

#	Conformity index reirradiation plan		Field 1			Field 2			Field 3			Field 4		
	Photons	Protons	Gantry angle[a]	Couch angle	Range shifter	Gantry angle	Couch angle	Range shifter	Gantry angle	Couch angle	Range shifter	Gantry angle	Couch angle	Range shifter
1	0.54	0.63	30	330	no	330	30	no	290	340	5 cm	70	20	5 cm
2	0.68	0.58	320	45	5 cm	40	315	5 cm						
3	0.6	0.69	307.4	350.8	5 cm	275.9	25.1	5 cm						
4	0.61	0.54	120	340	5 cm	240	20	5 cm						
5	0.58	0.65	75	360	5 cm	113.8	311.4	5 cm	201.1	27.1	5 cm			
6	0.86	0.37	135	0	5 cm	180	0	5 cm	100	275	5 cm			
7	0.58	0.53	90	325	5 cm	270	35	5 cm						
8	0.63	0.5	213.2	28	5 cm	145.4	320.8	5 cm						
9	0.64	0.49	244.2	346.9	5 cm	309.4	42	5 cm						

[a]Gantry and couch angle are in degrees.

RESULTS

Overview of the patients

Nine patients re-irradiated for recurrent meningioma between 2014 and 2017 were included in this analysis (Table 2). The mean age at re-irradiation was 62.9 ± 12.5 years and the mean time interval between radiation treatments was 45.3 ± 41.1 months. Location of the meningioma was convex in five cases (55.6%), parafalcine in three cases (33.3%) and tentorial in one case (11.1%). The mean PTV was 68.8 ± 49.7 and 43.5 ± 44.5 ccm for the initial and the secondary plan for recurrent disease, respectively. In five out of nine cases (55.6%), there was a partial overlap between the initial and the recurrence PTV. The mean overlap in these cases was 47.1 ± 21.0%. In the remaining four cases (44.4%), the PTV of the recurrence had no overlap with the initial PTV (Figure 1). The dose given in the initial treatment was 60 Gy (30 × 2 Gy) in five cases (55.6%), 59.4 Gy (33 × 1.8 Gy) in two cases (22.2%), 54 Gy (30 × 1.8 Gy) in one case (11.1%) and 52.2 Gy (29 × 1.8 Gy) in one case (11.1%).

Organs at risk

The average mean dose of each specified OAR (Table 3) was higher for the accumulated photon plans than for the accumulated proton plans for all nine patients. This difference was statistically significant for brain–-brainstem (15.5 ± 6.8 Gy *vs* 13.7 ± 5.8 Gy, $p < 0.01$), brainstem (8.2 ± 10.0 Gy *vs* 7.1 ± 9.4 Gy, $p < 0.01$), chiasm (13.2 ± 15.9 Gy *vs* 11.0 ± 13.5 Gy, $p < 0.01$), left optic nerve (10.8 ± 14.4 Gy *vs* 10.0 ± 13.9 Gy, $p < 0.01$), right optic nerve (13.0 ± 18.4 Gy *vs* 12.3 ± 18.2 Gy, $p < 0.01$), left hippocampus (9.5 ± 11.7 Gy *vs* 7.5 ± 11.0 Gy, $p < 0.01$), pituitary gland (15.1 ± 13.9 Gy, $p < 0.01$) and left cochlea (8.4 ± 14.1 Gy *vs* 7.6 ± 14.0 Gy, $p < 0.01$). The doses to the left hippocampus (14.8 ± 20.7 Gy *vs* 14.8 ± 24.4 Gy, n.s.) and right cochlea (11.3 ± 20.4 Gy *vs* 10.7 ± 20.8 Gy) were not statistically significantly different.

Similarly, the average maximum doses to the OARs (Table 3) were statistically significantly lower for the accumulated proton plans in most of the analyzed OARs (chiasm: 20.9 ± 24.4 *vs* 18.5 ± 23.2 Gy, $p < 0.01$; left optic nerve: 17.6 ± 22.6 *vs* 16.0 ± 21.8 Gy, $p < 0.01$; left hippocampus: 19.3 ± 20.1 *vs* 16.2 ± 19.6 Gy, $p < 0.01$; right hippocampus: 24.9 ± 33.4 *vs* 23.4 ± 33.6 Gy, $p < 0.05$; pituitary gland: 19.5 ± 24.8 *vs* 17.6 ± 23.6 Gy, $p < 0.01$; left cochlea: 10.1 ± 16.9 *vs* 9.3 ± 16.8 Gy). There was no statistically significant difference ($p > 0.05$) in average maximum dose to brain–brainstem (105.1 ± 20.4 Gy *vs* 105.3 ± 19.9 Gy, $p > 0.1$.), brainstem (24.3 ± 29.9 Gy *vs* 21.7 ± 31.8 Gy, $p > 0.05$), right optic nerve (18.8 ± 23.8 Gy *vs* 18.3 ± 24.7 Gy, $p > 0.05$) and right cochlea (13.0 ± 22.1 Gy *vs* 12.7 ± 23.7 Gy, $p > 0.1$).

Looking at the doses to the OARs in each individual case (Figure 2), depending on initial tumor and recurrent tumor location, more pronounced differences were identified. Especially in cases number 1, 3 and 6, larger differences in OAR doses for brainstem, chiasm, optic nerves, and cochlea were observed. In Case 1, the brainstem maximum point dose (39.9 Gy *vs* 28.0 Gy), the chiasm maximum point dose (59.3 *vs* 48.9 Gy), the left optic nerve maximum point dose (56.3 *vs* 50.1 Gy) and the mean chiasm dose (46.1 *vs* 34.5 Gy) were in favor of the proton plan. In Case 3, the brainstem maximum point dose (87.5 *vs* 92.6 Gy) and

Table 2. Patient characteristics

Case	Interval between radiation in months	Age at re-irradiation in years	WHO grading	Tumor location	Dose and fractions, initial radiation in Gy	Volume initial PTV in ccm	Volume re-irradiation PTV in ccm	Percentage of overlap initial and re-irradiation PTV
1	104	43	II	Convex	60 (30 × 2)	86.1	134.9	11.6
2	76	64	II	Convex	60 (30 × 2)	33.3	16.1	0
3	13	75	II	Tentorial, Right	60 (30 × 2)	58.2	7.3	0
4	49	74	I	Parafalcine	54 (30 × 1.8)	27	24.2	68.2
5	13	45	II	Convex	59.4 (33 × 1.8)	178.3	44.6	0
6	18	73	II	Parafalcine	59.4 (33 × 1.8)	88.3	101.9	51.1
7	21	60	II	Parafalcine	60 (30 × 2)	29	14.6	60.6
8	109	74	II	Convex	52.2 (29 × 1.8)	92.8	18.4	44
9	5	58	II	Convex	60 (30 × 2)	26.1	29.9	0

the right cochlea maximum point dose (65.6 *vs* 70.7 Gy) were in favor of the photon plan. In Case 6, the brainstem maximum point dose (13.8 Gy *vs* 1.8 Gy), the chiasm maximum point dose (9.0 Gy *vs* 0.9 Gy), the left optic nerve maximum point dose (6.3 Gy *vs* 0.8 Gy), the right optic nerve maximum point dose (4.7 Gy *vs* 0.7 Gy), and the mean chiasm dose (6.4 Gy *vs* 0.7 Gy) were in favor of the proton plan.

V100, V90 and V72

The accumulated dose of 100 Gy was reached in seven out of nine cases (77.8%) for both the proton and the photon plans. In all these cases, the V100 was larger for the proton plans than the photon plans, while the dose coverage of the PTV was equal. The mean V100 was 6.9 ± 9.1 and 10.3 ± 9.6 ccm for the accumulated photon and proton plan, respectively ($p < 0.05$). Similarly, the V90 and V72 volumes were significantly smaller for the photon plans than for the proton plans (Figure 3). The V90 was 32.7 ± 34.7 ccm for photons *vs* 43.8 ± 41.4 ccm for protons ($p < 0.05$). The V72 was 57.6 ± 71.4 ccm for photons *vs* 70.5 ± 65.5 ccm for protons ($p < 0.05$).

Integral dose

For the re-irradiation plans only, the integral dose and the total dose to the brain excluding the PTV were analyzed (Table 3 and Figure 4). In all nine cases, the integral dose was lower for the proton plans than for the photon plans. The mean integral dose for protons was reduced by 48.6% with respect to the photon plans (12.4 ± 12.7 Gy *vs* 6.4 ± 6.0 Gy, $p < 0.01$). The mean total dose received by the brain, excluding the PTV, was 57.7% less for protons compared to photons (6.4 ± 6.2 Gy *vs* 2.7 ± 2.5 Gy, $p < 0.01$).

Case specific analysis

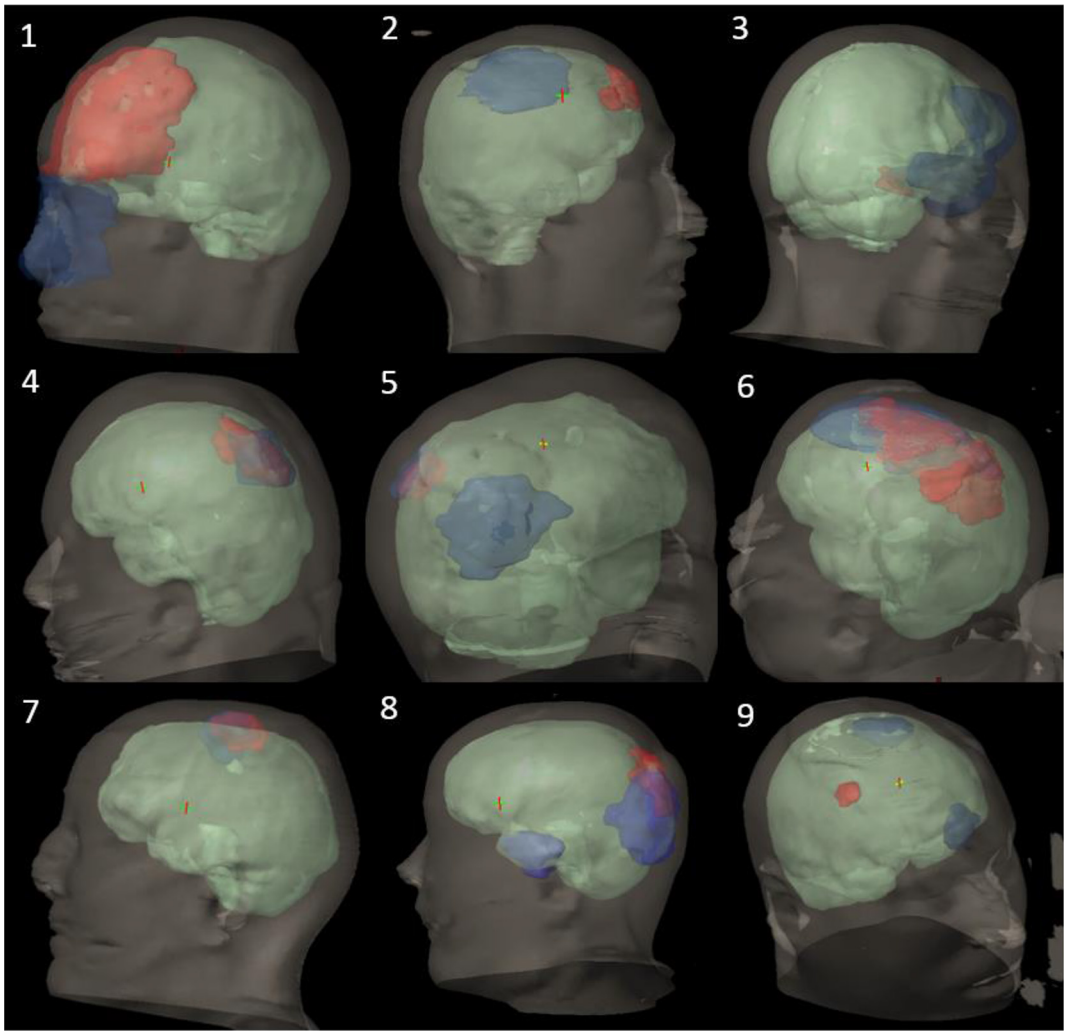
Despite the volumes receiving high doses (V100, V90 and V72) being smaller for the photon plans (Figure 3) and the integral doses being smaller for the proton plans, the area in which a specific plan shows superiority is largely dependent on the size, location and shape of the target (Figure 5). While Case 6 had a larger PTV (101.9 ccm) protruding deeper into the brain with concave parts, Case 7 had a smaller, spherical and more superficially located target (14.6 ccm). Even though, the high dose volumes, *i.e.* V100 and V90, are still bigger for the proton plan in Case 6 (26.2 ccm *vs* 29.1 ccm and 104.0 *vs* 131.2 ccm), the V72 (224.3 ccm *vs* 220.6 ccm, Figure 3) and the integral dose brain dose are lower (17.7 Gy *vs* 8.7 Gy, Figure 4).

DISCUSSION

The goal of this study was to provide a dosimetric comparison between protons and photons for re-irradiation of recurrent meningioma. While the brain volume receiving 100, 90 and 70 Gy was higher for the proton plans, significantly better dose sparing of average mean and maximum doses to the majority of OARs could be achieved for protons. Additionally, the integral dose and total brain dose were roughly 50% lower for the proton plans compared with the photon plans.

Brain barrier disorder is a frequently observed late side-effect after intracranial re-irradiation and predominantly occurs

Figure 1. Three-dimensional representation of the tumor locations of the primary treatment.



within a few years after treatment.[39–43] The probability to develop a brain barrier disorder depends on the prescribed RT dose and the volume affected by high RT doses as mentioned.[44,45] It has been shown that the incidence of brain barrier disorders increases from 5 to 10% at doses of 72 *vs* 90 Gy.[28] Schlampp et al identified temporal lobe necrosis in 5% of the patients who received heavy ions with RT doses of 68.8 Gy (RBE) on the skull base *vs* 50% when irradiated with 87.3 Gy (RBE).[44] Thus, for accumulated doses up to 100 Gy EQD2, this rate cannot be disregarded;[20,46] the higher the volume receiving these doses, the higher the chances of a brain necrosis. Many of the proton planning studies reported that proton plans achieve higher conformity due to the lack of exit dose and the steep gradient in the distal edge and are, therefore, better at sparing previously irradiated areas.[4,16,17,26–33] Our results showed that the V100, V90 and V72, predictors of brain injury, were all in favor to the photon plans showing superior high dose conformity. Similar results were found in a proton–photon comparison study in rectal cancer by Berman et al, which used the double scatter technique[35] and in a dosimetric evaluation in non-small cell lung cancer performed by Macdonald et al..[47] The reason for the inferior dose gradient of the proton plans in the current study are the inferior lateral penumbra of pencil beam scanning and the range shifter that was used in all of the plans. The lateral penumbra of spot scanned proton beams is characterized by a less steep dose fall-off compared to the dose fall-off at the distal edge and is considered inferior to what can be achieved with photons. Especially, in the lower energies used for superficial dose deposition the lateral penumbra is wider.[48] The majority of the dose bath surrounding the target is made up by the lateral penumbra. Therefore, the high dose area surrounding the target will only have a real benefit of the Bragg peak on the side—distally from the proton beam. In the case of re-irradiation, where one wants to keep the high dose area as small as possible isotropically around the target, the typical physical characteristics of protons need to be reconsidered. The use of the range shifter will have an impact on the spot size.[49] The typical spot size used for these plans was 0.425 cm. An increase in the spot size will result in a spread out of the dose gradient. Regarding the range shifter used in these plans, the dose gradient from 100 to 50% of the dose will be approximately 25–30% narrower when no range shifter is used. Without the range shifter, there will still be a slight advantage for the high dose regions for photons, but the intersect of the integral dose will be shifted towards the right and the dosimetric advantage will start at a higher dose.

Table 3. Overview of the dose volume analysis on the EQD2 accumulated plans

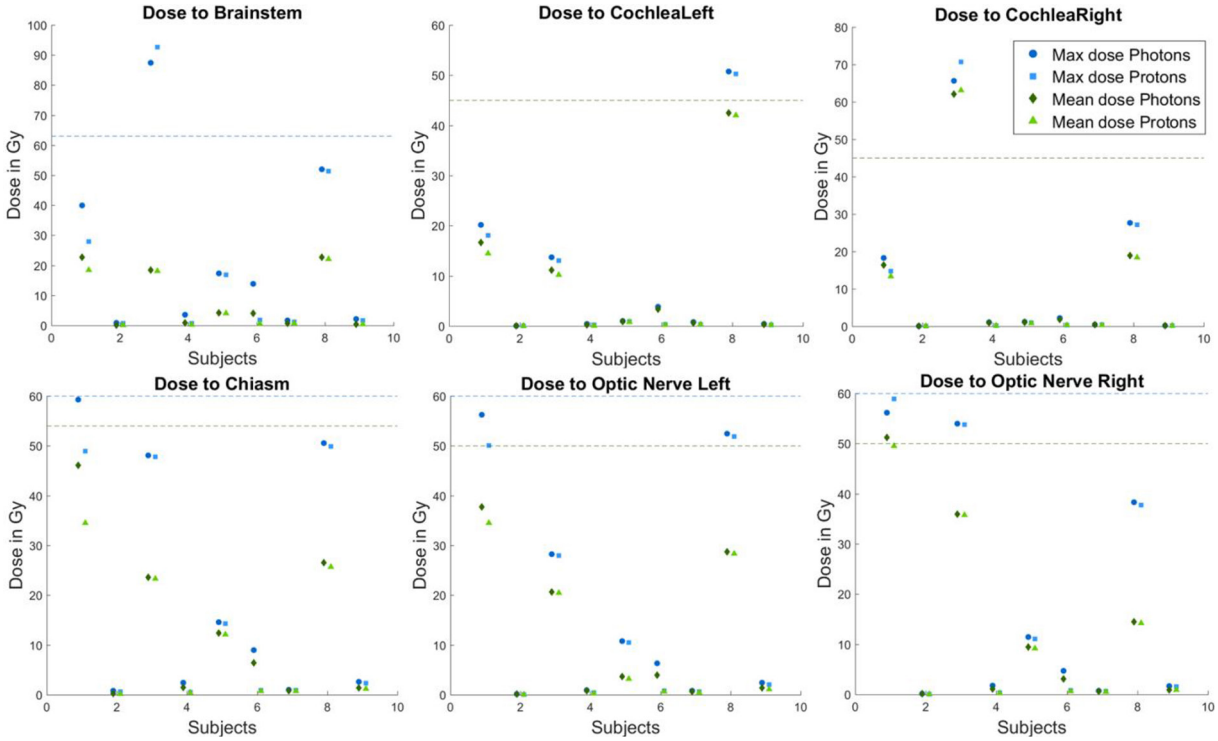
		EQD2 of accumulated photon reirradiation plan (stdv)	EQD2 of accumulated proton reirradiation plan (stdv)	Significance according to Wilcoxon signed-ranks test
Brain–brainstem	*Max dose*	105.1 (±20.4)	105.3 (±19.9)	not significant
	Mean dose	15.5 (±6.8)	13.7 (±5.8)	$p < 0.01$
Brainstem	*Max dose*	24.3 (±30.0)	21.7 (±31.8)	not significant
	Mean dose	8.2 (±10.0)	7.1 (±9.4)	$p < 0.01$
Chiasm	*Max dose*	20.9 (±24.4)	18.5 (±23.2)	$p < 0.01$
	Mean dose	13.2 (±15.9)	11.0 (±13.5)	$p < 0.01$
Optic nerve left	*Max dose*	17.6 (±22.6)	16.0 (±21.8)	$p < 0.01$
	Mean dose	10.8 (±14.4)	9.9 (±13.9)	$p < 0.01$
Optic nerve right	*Max dose*	18.8 (±23.8)	18.3 (±24.7)	not significant
	Mean dose	13.0 (±18.4)	12.3 (±18.2)	$p < 0.01$
Hippocampus left	*Max dose*	19.3 (±20.1)	16.2 (±19.6)	$p < 0.01$
	Mean dose	9.5 (±11.7)	7.5 (±11.0)	$p < 0.01$
Hippocampus right	*Max dose*	24.9 (±33.4)	23.4 (±33.6)	$p < 0.05$
	Mean dose	14.8 (±20.7)	14.7 (±24.4)	not significant
Pituitary gland	*Max dose*	19.5 (±24.8)	17.6 (±23.6)	$p < 0.01$
	Mean dose	15.1 (±20.6)	13.9 (±20.2)	$p < 0.01$
Cochlea left	*Max dose*	10.1 (±16.8)	9.3 (±16.8)	$p < 0.01$
	Mean dose	8.4 (±14.1)	7.6 (±14.0)	$p < 0.01$
Cochlea right	*Max dose*	13.0 (±22.1)	12.7 (±23.7)	not significant
	Mean dose	11.3 (±20.4)	10.7 (±20.8)	not significant
		Volume in ccm (stdv)		
V100		5.4 (±8.5)	8.0 (±9.5)	$p < 0.05$
V90		25.4 (±33.4)	30.1 (±40.7)	$p < 0.05$
V70		51.2 (±69.5)	62.6 (±65.6)	$p < 0.05$
		Integral dose in Gy (stdv) to the single reirradiation plans		
		Photons	**Protons**	
Total integral dose		12.4 (±12.7)	6.4 (±6.0)	$p < 0.01$
Dose to brain-PTV		6.4 (±6.2)	2.7 (±2.5)	$p < 0.01$
		Conformity index of the reirradiation plans		
Conformity index		0.63 (±0.09)	0.55 (±0.1)	not significant

PTV, planning target volume.

The dose gradient could be slightly improved by adjusting the settings for the NTO. However, this would come at the expense of the coverage and homogeneity of the dose in the target; thus, this possibility was limited.

Dose constraints for critical structures in the brain have been elaborated by the Radiation Therapy Oncology Group and Quantec after the pioneering work of Emami et al..[25,50–52] In the current study, OAR sparing was almost identical between protons and photons. In fact, the absolute difference in dose to OARs was only potentially clinically relevant on an individual level. In two cases, protons were in favor, and in one case, photons were favorable. In the remaining six cases, dosimetric results were comparable. More recently, it has been discovered that, apart from fraction size and radiation volume,[53,54] the doses to the hippocampi are correlated with cognitive impairment.[55,56] While, the proton plans achieved a better hippocampal sparing in our analysis, the absolute difference was negligible. However, the integral dose to the brain, another predictor of neurocognitive impairment, was clearly superior with the proton plans.

Figure 2. Plots of the max and mean doses of the accumulated EQD2 plans with photons and protons for different organs at risk.



Therefore, determining the preferable treatment modality is extremely case specific. This result demonstrates the importance of individual plan comparison for optimal patient selection for proton therapy, but individual plan comparison costs time and resources; thus, is not desirable for every patient. The goal should be to determine guidelines, in which, based on case specific properties, patients could be selected for plan comparison. In other words, we should be able to select, prior to plan comparison, which patients will definitely benefit from protons and which patients will definitely not. In the remaining "borderline" cases plan comparison can provide the solution. In specific cases in this study, we noticed that the advantage for protons is associated with the size and shape of the tumor as well as the location and the relative distance to certain OARs. Consequently, in a recent study on reirradiation with particle therapy, published by El Shafie et al, the majority of lesions where located at the skull base, which is typically is a good location for particle therapy.[34] *In silico* studies could help to discover and elaborate such properties to determine specific guidelines based on size, shape and location of the target. Together with other parameters such as prognosis, patient condition and the type of alternative photon treatment it can be determined, if a specific case should be treated with photons, protons or needs a plan comparison.

There are a few limitations to our study. For an optimal comparison between the two modalities we have chosen the same PTV, planning platform and fractionation scheme for both the proton and photon plans. In an actual clinical setting, the margins to get to a PTV might differ for a photon or a proton treatment, resulting in different target sizes. Also, the fractionation of 15 × 3 Gy might not be the optimal choice for both photon and proton re-irradiations. The treatment planning data of the photon plans are performed on a clinically used and commissioned platform. The beam data is adopted from the actual re-irradiated plan and clinically verified. The proton plans, however, were performed on modeled beam data and these plans were not verified for clinical

Figure 3. Bar plots of the volumes outside the PTV receiving 100, 90 and 72 Gy (EQD2) in accumulated dose for the photon plans (blue bars) and the proton plans (green bars). PTV, planning target volume.

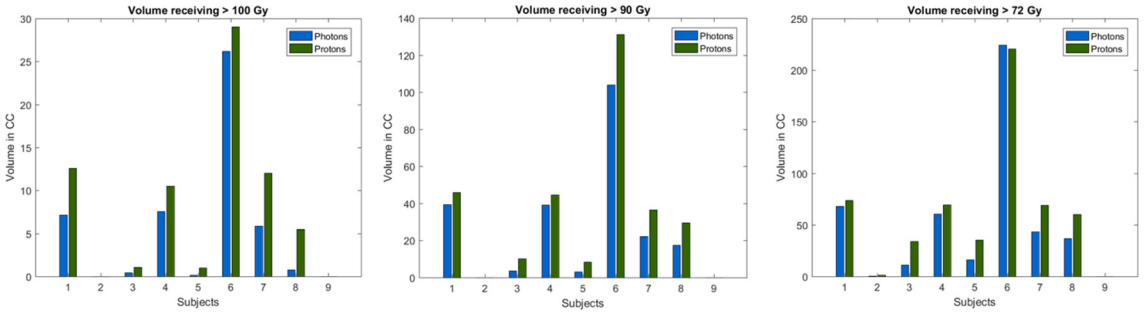


Figure 4. Bar plots of the integral dose of the re-irradiation plans. PTV,planning target volume.

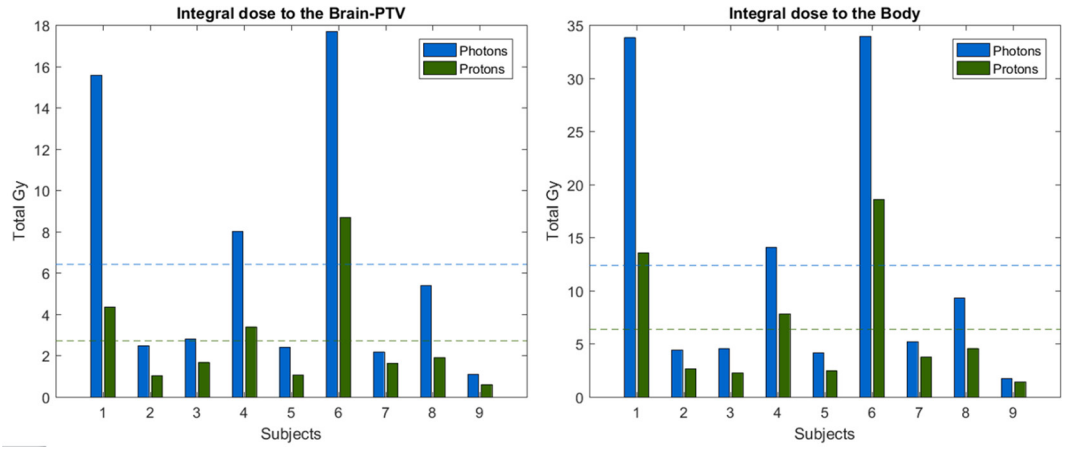
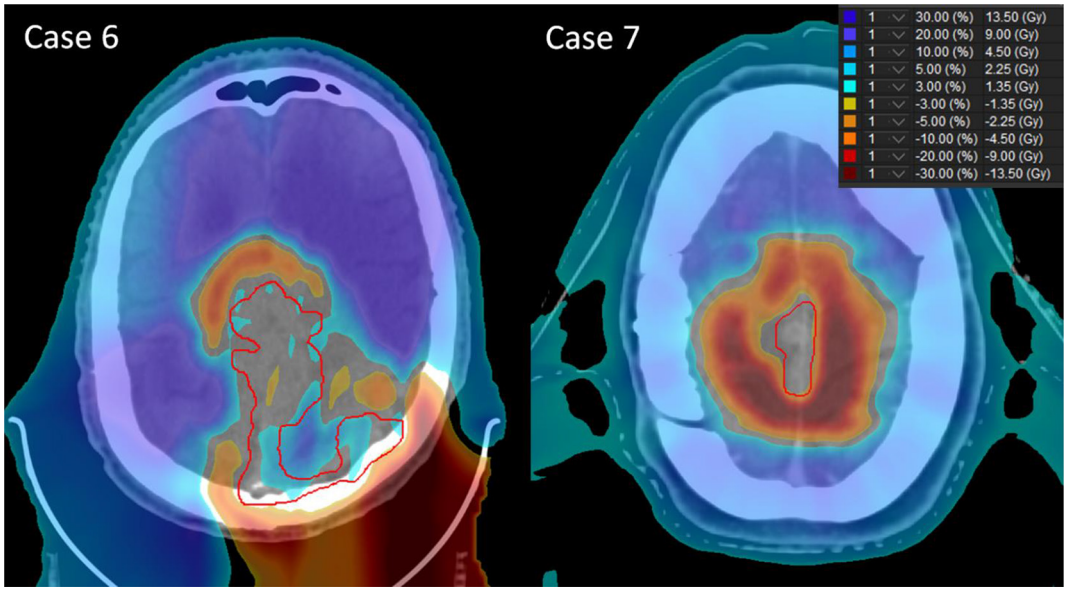


Figure 5. Dose difference mapping of the photon minus the proton re-irradiation plans of Case 6 and Case 7.



use. Furthermore, only one range shifter of 5 cm thickness was available, while in some cases this might have been abundant.

CONCLUSION

The dosimetric results of the accumulated dose for a re-irradiation with protons and with photons were very similar in this cohort. In general, the photon plans had a steeper dose falloff directly outside the target and were superior in minimizing the high dose volumes. The proton plans achieved a lower integral dose. Clinically relevant OAR sparing was extremely case specific, and it is recommended that the treatment modality should be assessed on an individual basis.

REFERENCES

1. Choi JH. Outcomes following re-irradiation for symptomatic brain metastasis. *J Cancer Sci Ther* 2015; **7**: 308–11.
2. Kirkpatrick JP. Sampson JH: recurrent malignant gliomas. *Semin Radiat Oncol* 2014; **24**: 289–98.
3. Bauman GS, Sneed PK, Wara WM, Stalpers LJ, Chang SM, McDermott MW, et al. Reirradiation of primary CNS tumors. *Int J Radiat Oncol Biol Phys* 1996; **36**: 433–41. doi: https://doi.org/10.1016/S0360-3016(96)00315-X
4. Mizumoto M, Okumura T, Ishikawa E, Yamamoto T, Takano S, Matsumura A, et al. Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy. Technical Considerations based on experience at a single institution. *Strahlenther Onkol* 2013; **189**: 656–63. doi: https://doi.org/10.1007/s00066-013-0390-6
5. Nieder C, Andratschke NH, Grosu AL. Re-irradiation for recurrent primary brain tumors. *Anticancer Res* 2016; **36**: 4985–96.

doi: https://doi.org/10.21873/anticanres.11067
6. Ang KK, Jiang GL, Guttenberger R, Thames HD, Stephens LC, Smith CD, et al. Impact of spinal cord repair kinetics on the practice of altered fractionation schedules. *Radiother Oncol* 1992; **25**: 287–94. doi: https://doi.org/10.1016/0167-8140(92)90249-T
7. Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. *Semin Radiat Oncol* 2000; **10**: 200–9. doi: https://doi.org/10.1053/srao.2000.6593
8. Bouffet E, Hawkins CE, Ballourah W, Taylor MD, Bartels UK, Schoenhoff N, et al. Survival benefit for pediatric patients with recurrent ependymoma treated with reirradiation. *Int J Radiat Oncol Biol Phys* 2012; **83**: 1541–8. doi: https://doi.org/10.1016/j.ijrobp.2011.10.039
9. Fogh SE, Andrews DW, Glass J, Curran W, Glass C, Champ C, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. *J Clin Oncol* 2010; **28**: 3048–53. doi: https://doi.org/10.1200/JCO.2009.25.6941
10. Huang Z, Sun B, Shen G, Cha L, Meng X, Wang J, et al. Brain metastasis reirradiation in patients with advanced breast cancer. *J Radiat Res* 2017; **58**: 142–8. doi: https://doi.org/10.1093/jrr/rrw087
11. Lobón MJ, Bautista F, Riet F, Dhermain F, Canale S, Dufour C, et al. Re-irradiation of recurrent pediatric ependymoma: modalities and outcomes: a twenty-year survey. *Springerplus* 2016; **5**: 879. doi: https://doi.org/10.1186/s40064-016-2562-1
12. Schnell O, Thorsteinsdottir J, Fleischmann DF, Lenski M, Abenhardt W, Giese A, et al. Re-irradiation strategies in combination with bevacizumab for recurrent malignant glioma. *J Neurooncol* 2016; **130**: 591–9. doi: https://doi.org/10.1007/s11060-016-2267-x
13. Amelio D, Amichetti M. Radiation therapy for the treatment of recurrent glioblastoma: an overview. *Cancers* 2012; **4**: 257–80. doi: https://doi.org/10.3390/cancers4010257
14. Amichetti M, Amelio D. A review of the role of re-irradiation in recurrent high-grade glioma (HGG. *Cancers* 2011; **3**: 4061–89. doi: https://doi.org/10.3390/cancers3044061
15. Bahl A, Kumar M, Sharma DN, Jothy Basu KS, Jaura MS, Rath GK, et al. Reirradiation for progressive brain metastases. *J Can Res Ther* 2009; **5**: 161–4. doi: https://doi.org/10.4103/0973-1482.57120
16. Eaton BR, Chowdhry V, Weaver K, Liu L, Ebb D, MacDonald SM, et al. Use of proton therapy for re-irradiation in pediatric intracranial ependymoma. *Radiother Oncol* 2015; **116**: 301–8. doi: https://doi.org/10.1016/j.radonc.2015.07.023
17. Galle JO, McDonald MW, Simoneaux V, Buchsbaum JC. Reirradiation with proton therapy for recurrent gliomas. *International Journal of Particle Therapy* 2015; **2**: 11–18. doi: https://doi.org/10.14338/THEIJPT-14-00029.1
18. Nieder C, Astner ST, Mehta MP, Grosu AL, Molls M. Improvement, clinical course, and quality of life after palliative radiotherapy for recurrent glioblastoma. *Am J Clin Oncol* 2008; **31**: 300–5. doi: https://doi.org/10.1097/COC.0b013e31815e3fdc
19. Scholtyssek F, Zwiener I, Schlamann A, Seidel C, Meixensberger J, Bauer M, et al. Reirradiation in progressive high-grade gliomas: outcome, role of concurrent chemotherapy, prognostic factors and validation of a new prognostic score with an independent patient cohort. *Radiat Oncol* 2013; **8**: 161. doi: https://doi.org/10.1186/1748-717X-8-161
20. Sminia P, Mayer R. External beam radiotherapy of recurrent glioma: radiation tolerance of the human brain. *Cancers* 2012; **4**: 379–99. doi: https://doi.org/10.3390/cancers4020379
21. Vargo JA, Wegner RE, Heron DE, Ferris RL, Rwigema J-CM, Quinn A, et al. Stereotactic body radiation therapy for locally recurrent, previously irradiated nonsquamous cell cancers of the head and neck. *Head Neck* 2012; **34**: 1153–61. doi: https://doi.org/10.1002/hed.21889
22. Veninga T, Langendijk HA, Slotman BJ, Rutten EHJM, van der Kogel AJ, Prick MJJ, et al. Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. *Radiotherapy and Oncology* 2001; **59**: 127–37. doi: https://doi.org/10.1016/S0167-8140(01)00299-7
23. Nahed BV, Redjal N, Brat DJ, Chi AS, Oh K, Batchelor TT, et al. Management of patients with recurrence of diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2015; **125**: 609–30. doi: https://doi.org/10.1007/s11060-015-1910-2
24. Ryu S, Buatti JM, Morris A, Kalkanis SN, Ryken TC, Olson JJ, et al. The role of radiotherapy in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2014; **118**: 489–99. doi: https://doi.org/10.1007/s11060-013-1337-6
25. Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, et al. Radiation Dose–Volume effects in the brain. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S20–S27. doi: https://doi.org/10.1016/j.ijrobp.2009.02.091
26. Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. *Int J Radiat Oncol Biol Phys* 2016; **95**: 386–95. doi: https://doi.org/10.1016/j.ijrobp.2016.02.036
27. Chao H-H, Berman AT, Simone CB, Ciunci C, Gabriel P, Lin H, et al. Multi-institutional prospective study of reirradiation with proton beam radiotherapy for locoregionally recurrent non-small cell lung cancer. *J Thorac Oncol* 2017; **12**: 281–92. doi: https://doi.org/10.1016/j.jtho.2016.10.018
28. Fernandes A, Berman AT, Mick R, Both S, Lelionis K, Lukens JN, et al. A prospective study of proton beam reirradiation for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2016; **95**: 483–7. doi: https://doi.org/10.1016/j.ijrobp.2015.12.005
29. Marucci L, Lane AM, Li W, Egan KM, Gragoudas ES, Adams JA, et al. Conservation treatment of the eye: conformal proton reirradiation for recurrent uveal melanoma. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1018–22. doi: https://doi.org/10.1016/j.ijrobp.2005.09.035
30. McAvoy S, Ciura K, Wei C, Rineer J, Liao Z, Chang JY, et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. *Int J Radiat Oncol Biol Phys* 2014; **90**: 819–27. doi: https://doi.org/10.1016/j.ijrobp.2014.07.030
31. McDonald MW, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. *Int J Radiat Oncol Biol Phys* 2013; **87**: 1107–14. doi: https://doi.org/10.1016/j.ijrobp.2013.09.038
32. McDonald MW, Zolali-Meybodi O, Lehnert SJ, Estabrook NC, Liu Y, Cohen-Gadol AA, et al. Reirradiation of recurrent and second primary head and neck cancer with proton therapy. *Int J Radiat Oncol Biol Phys* 2016; **96**: 808–19. doi: https://doi.org/10.1016/j.ijrobp.2016.07.037
33. Phan J, Sio TT, Nguyen TP, Takiar V, Gunn GB, Garden AS, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys* 2016; **96**: 30–41. doi: https://doi.org/10.1016/j.ijrobp.2016.03.053
34. El Shafie RA, Czech M, Kessel KA, Habermehl D, Weber D, Rieken S, et al. Evaluation of particle radiotherapy for the re-irradiation of recurrent intracranial meningioma. *Radiat Oncol* 2018; **13**: 86. doi: https://doi.org/10.1186/s13014-018-1026-x

35. Berman AT, Both S, Sharkoski T, Goldrath K, Tochner Z, Apisarnthanarax S, et al. Proton reirradiation of recurrent rectal cancer: Dosimetric comparison, toxicities, and preliminary outcomes. *International Journal of Particle Therapy* 2014; **1**: 2–13. doi: https://doi.org/10.14338/IJPT.13-00002.1
36. Scoccianti S, Detti B, Gadda D, Greto D, Furfaro I, Meacci F, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. *Radiother Oncol* 2015; **114**: 230–8. doi: https://doi.org/10.1016/j.radonc.2015.01.016
37. Jacques R, Taylor R, Wong J, McNutt T. Towards real-time radiation therapy: GpU accelerated superposition/convolution. *Comput Methods Programs Biomed* 2010; **98**: 285–92. doi: https://doi.org/10.1016/j.cmpb.2009.07.004
38. Langner UW, Eley JG, Dong L, Langen K. Comparison of multi-institutional Varian ProBeam pencil beam scanning proton beam commissioning data. *J Appl Clin Med Phys* 2017; **18**: 96–107. doi: https://doi.org/10.1002/acm2.12078
39. Chew NK, Sim BF, Tan CT, Goh KJ, Ramli N, Umapathi P. Delayed post-irradiation bulbar palsy in nasopharyngeal carcinoma. *Neurology* 2001; **57**: 529–31. doi: https://doi.org/10.1212/WNL.57.3.529
40. Hsiao K-Y, Yeh S-A, Chang C-C, Tsai P-C, Wu J-M, Gau J-S. Cognitive function before and after intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 2010; **77**: 722–6. doi: https://doi.org/10.1016/j.ijrobp.2009.06.080
41. Lam T-C, Wong FCS, Leung T-W, Ng SH, Tung SY. Clinical outcomes of 174 nasopharyngeal carcinoma patients with radiation-induced temporal lobe necrosis. *Int J Radiat Oncol Biol Phys* 2012; **82**: e57–65. doi: https://doi.org/10.1016/j.ijrobp.2010.11.070
42. Teo PM, Leung SF, Chan AT, Leung TW, Choi PH, Kwan WH, et al. Final report of a randomized trial on altered-fractionated radiotherapy in nasopharyngeal carcinoma prematurely terminated by significant increase in neurologic complications. *Int J Radiat Oncol Biol Phys* 2000; **48**: 1311–22. doi: https://doi.org/10.1016/S0360-3016(00)00786-0
43. Yeh S-A, Ho J-T, Lui C-C, Huang Y-J, Hsiung C-Y, Huang E-Y. Treatment outcomes and prognostic factors in patients with supratentorial low-grade gliomas. *Br J Radiol* 2005; **78**: 230–5. doi: https://doi.org/10.1259/bjr/28534346
44. Schlampp I, Karger CP, Jäkel O, Scholz M, Didinger B, Nikoghosyan A, et al. Temporal lobe reactions after radiotherapy with carbon ions: incidence and estimation of the relative biological effectiveness by the local effect model. *Int J Radiat Oncol Biol Phys* 2011; **80**: 815–23. doi: https://doi.org/10.1016/j.ijrobp.2010.03.001
45. Pehlivan B, Ares C, Lomax AJ, Stadelmann O, Goitein G, Timmermann B, et al. Temporal lobe toxicity analysis after proton radiation therapy for skull base tumors. *Int J Radiat Oncol Biol Phys* 2012; **83**: 1432–40. doi: https://doi.org/10.1016/j.ijrobp.2011.10.042
46. Mayer R, Sminia P. Reirradiation tolerance of the human brain. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1350–60. doi: https://doi.org/10.1016/j.ijrobp.2007.08.015
47. Macdonald OK, Kruse JJ, Miller JM, Garces YI, Brown PD, Miller RC, et al. Proton beam radiotherapy versus three-dimensional conformal stereotactic body radiotherapy in primary peripheral, early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2009; **75**: 950–8. doi: https://doi.org/10.1016/j.ijrobp.2009.04.023
48. Safai S, Bortfeld T, Engelsman M. Comparison between the lateral penumbra of a collimated double-scattered beam and uncollimated scanning beam in proton radiotherapy. *Phys Med Biol* 2008; **53**: 1729–50. doi: https://doi.org/10.1088/0031-9155/53/6/016
49. Shen J, Liu W, Anand A, Stoker JB, Ding X, Fatyga M, et al. Impact of range shifter material on proton pencil beam spot characteristics. *Med Phys* 2015; **42**: 1335–40. doi: https://doi.org/10.1118/1.4908208
50. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; **21**: 109–22. doi: https://doi.org/10.1016/0360-3016(91)90171-Y
51. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S10–S19. doi: https://doi.org/10.1016/j.ijrobp.2009.07.1754
52. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S3–S9. doi: https://doi.org/10.1016/j.ijrobp.2009.09.040
53. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: a review. *Front Oncol* 2012; **2**: 73. doi: https://doi.org/10.3389/fonc.2012.00073
54. Laack NN, Brown PD. Cognitive sequelae of brain radiation in adults. *Semin Oncol* 2004; **31**: 702–13. doi: https://doi.org/10.1053/j.seminoncol.2004.07.013
55. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys* 2013; **85**: 348–54. doi: https://doi.org/10.1016/j.ijrobp.2012.11.031
56. Gondi V, Tomé WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol* 2010; **97**: 370–6. doi: https://doi.org/10.1016/j.radonc.2010.09.013